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Strategies for the management of pulmonary arterial hypertension in patients with congenital heart disease

Nathalie Liew[1], Zoya Rashid[1] and Robert Tulloh[1,2]*

Abstract

Background: Pulmonary hypertension (PH) is commonly seen in adults who have congenital heart disease (CHD). Therapy is available for pulmonary arterial hypertension (PAH) and has greatly benefitted many patients with PAH related to CHD (PAH-CHD) over the last 15 years, with evidence of improved quality of life and prognosis in those with Eisenmenger syndrome and repaired PAH-CHD.

In this review, we describe the standard management and advanced therapies for PAH, which are available in specialist PH centres around the UK and Ireland, and how these are used in PAH-CHD. Decisions around the choice of therapy are governed by commissioning and available evidence.

Conclusion: We explain the different pathways for action and the variety of medications now at our disposal to help this important group of patients.

Keywords: Pulmonary hypertension, Congenital heart disease, Sildenafil, Tadalafil, Bosentan, Ambrisentan, Macitentan, Epoprostenol, Iloprost, Treprostinil

Background

Eisenmenger syndrome (ES) is a multisystem disorder characterised by severely elevated pulmonary arterial pressures and pulmonary vascular resistance leading to cyanosis due to reversal of blood flow from a previous left to right shunt. It represents an advanced form of PAH associated with CHD [1, 2] that can lead to multiorgan involvement and systemic complications related to the underlying disease, the PH and also the chronic hypoxaemia. Despite ongoing advances in care, approximately 10% of patients with CHD develop PAH. PAH-CHD is now one of the most common causes of PAH, along with idiopathic PAH and connective tissue disease-related PAH. The present clinical subclassification of PAH-CHD is now aligned with the 5th and 6th World Symposia

on PH (2013 and 2018) held in Nice, France [3, 4]. We now see at least four individual subgroups of PAH-CHD patients with their distinct phenotypes: A) Eisenmenger syndrome; B) Left-to-right shunts with mild-moderate PAH; C) PAH with small/coincidental defects; and D) Postoperative PAH.

Previous papers in this supplement, have detailed the classification, pathophysiology, investigation and standard treatment for PAH-CHD. Prior to 1995, the standard therapies for PAH-CHD were limited and mainly supportive. Standard regimens included calcium channel blockers (nowadays not recommended for PAH-CHD), oral anticoagulation, diuretics and oxygen supplementation, leading to eventual lung or heart-lung transplant. However, studies have shown little improvement in survival rates in most people under these standard therapies, and neither oxygen nor anticoagulation is routinely used in PAH-CHD. With better understanding of the biology of PAH, three groups of pulmonary vasodilators

* Correspondence: Robert.Tulloh@bristol.ac.uk
[1]Bristol Heart Institute and Bristol Medical School, Bristol, UK
[2]Department of Congenital Heart Disease Bristol BS2 8HW, UK

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have emerged as therapies for PAH. These include phosphodiesterase type 5 inhibitors (and soluble guanylate cyclase stimulators), endothelin receptor antagonists and prostacyclin analogues (or receptor agonists). Despite a significant improvement in functional capacity, morbidity and mortality in some PAH-CHD groups (namely groups A and D), the long-term effect on morbidity, mortality, as well health service utilisation remains somewhat uncertain.

This review provides a summary of key data on emerging treatments and the suitability of different classes of drugs and interventions for PAH-CHD patients. Standard therapy is provided in another paper in this supplement and will not be included here.

Advanced PAH-specific therapy

In PAH-CHD, left-right shunting causes an increase in pulmonary blood flow, exerting shear stress on the pulmonary endothelium and causing histopathological and pathobiological changes that are similar to those observed in other forms of PAH [2]. Endothelial dysfunction of the pulmonary vasculature plays a key role in the progression of PAH and is characterised by impaired synthesis of vasodilatory nitric oxide (NO) and prostacyclin, overproduction of vasoconstricting thromboxane A2 and endothelin. These observations have underpinned three therapeutic target pathways in PAH, which will be further evaluated in this review.

Phosphodiesterase type 5 inhibitors

Sildenafil is a phosphodiesterase type 5 inhibitor (PDE5i), which is widely used due to ease of use and low cost, that increases the level of cyclic guanosine monophosphate (cGMP) in the body [5]. The accumulation of cGMP then leads to a series of cellular changes that concludes with a decrease in intracellular calcium levels, improved right ventricular function and reduced vascular smooth muscle contraction [6]. In general practice the most frequent of the adverse reactions to the treatment are in order of frequency, vomiting, headache, bronchitis, pyrexia, pharyngitis, cough, diarrhoea and nasopharyngitis (nasal "stuffiness").

There is now good evidence for benefit in ES. Several studies have shown improvement in WHO functional class, and almost all of these have shown an increase in 6-min walk distance (6MWD) [7–13]. In addition, tadalafil, a longer acting PDE5i has been shown to improve WHO functional class, increase 6MWD and reduce PVR in this same group [14].

Soluble guanylate cyclase stimulator
Riociguat
A novel class of drugs targeting the NO pathway are the soluble guanylate cyclase (sGC) stimulators, with riociguat being the first to be approved. Riociguat facilitates the binding of sGC to NO by stabilising the NO-sGC bond. This compound acts independently from endogenous NO production and is able to increase intracellular cGMP levels by direct stimulation of sGC, provided the haem group of sGC remains active.

The PAH sGC-stimulator Trial-1 (PATENT-1) was a 12-week long, randomised, double-blind, placebo-controlled phase III clinical trial which enrolled a subgroup of 35 patients with PAH-CHD following cardiac surgery [15, 16]. Post hoc analysis showed considerable improvement (> 10%) in 6MWD and pulmonary vascular resistance (PVR) from baseline in patients who received riociguat (either low-dose 1.5 mg or high dose 2.5 mg three times daily). Other outcomes observed in this trial included an improvement in subjects' exercise capacity, haemodynamics, N-terminal pro brain natriuretic peptide (NT-proBNP) levels and WHO functional class. A second post hoc analysis was carried out in PATENT-2, an open-label long term extension of PATENT-1 where patients were followed up for a further 2 years [16]. In PATENT-2, 33 of the 35 patients with PAH-CHD enrolled in PATENT-1 were continued on long-term riociguat (2.5 mg three times daily) with the aim to assess safety and tolerability of the drug. Improvements in 6MWD in the treatment group of PATENT-1 were sustained at 2 years of PATENT-2 (an additional 18.7% improvement in the former 2.5 mg riociguat group). With regards to adverse effects, the incidence of syncope and hypotension (side effects that have been reported as frequent with riociguat) were relatively low in CHD patients.

At present, most studies on advanced PAH-specific therapies (including PDE5i and ERAs) only include closed defects or those specifically with ES and no studies have looked at those with persisting left to right shunts or those with small defects, making it difficult to draw comparisons. Several randomised controlled trials have included PAH-CHD with closed defects and have studied PAH therapies in ES, but there are very few data about treatments in left to right shunts and those patients with small defects. Riociguat has been approved both for the treatment of PAH and inoperable or persistent (after surgery) chronic thromboembolic pulmonary hypertension (CTEPH) but is mainly used in PAH-CHD for those who do not tolerate PDE5i as an alternative therapy [17].

Endothelin pathway and Endothelin receptor antagonists (ERA)

Endothelin 1 (ET-1) is a vasoactive peptide that plays a key role in the cardiovascular system. It works by exerting vasoconstrictor and mitogenic effects by binding to two distinct G-protein receptor sub-types in the pulmonary vascular smooth muscle, including ET-A and ET-B [18]. Plasma ET-1 concentrations in the PAH-

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CHD group were found to be significantly higher in the superior and inferior vena cava, right atrium, right ventricle, pulmonary artery and pulmonary vein.

Bosentan is an oral, dual ET-A and ET-B endothelin receptor antagonist (ERA) and the first molecule from this class to be synthesised. To date, it is the most well-studied drug used in the treatment of ES. Approved in 2001, joint guidelines from the European Society of Cardiology and European Respiratory Society recommend that bosentan therapy is initiated in ES [19]. The Bosentan Randomised Trial of Endothelin Antagonist THErapy-5 (BREATHE-5) study was the first trial designed as a multicentre, randomised, double-blind, placebo-controlled study evaluating the effect of bosentan in patients with ES [20]. Fifty-four patients > 12 years of age with WHO functional class III ES were enrolled; 37 received bosentan and 17 received placebo over 16 weeks. The 6MWD improved by 13% in the bosentan group and decreased by 3% in the placebo group. Similar favourable results have been reported in other controlled studies evaluating the effects of bosentan in PAH-CHD [21]. Furthermore, improvements in exercise capacity were maintained in the same cohort of patients following 24 additional weeks in an open-label extension of BREATHE-5 with the former placebo group experiencing an increase in 6MWD by 8.3% from baseline following bosentan therapy. With regards to adverse effects, peripheral oedema was the most common side effect occurring in 19% of patients on bosentan versus 6% on placebo. Other less common side effects reported were headache, palpitations, dizziness, and chest pain. One patient had to discontinue because of elevated liver enzymes > 5 times the upper limit of normal. This is consistent with other studies which showed that approximately 10% of patients had increases in hepatic aminotransferases and this was found to be dose dependent and reversible after dose reduction or withdrawal. For these reasons, patients on bosentan should have their liver function monitored monthly.

Other ERA
Macitentan is the newest ERA studied for the treatment of PAH. Like bosentan, macitentan acts on both ET-A and ET-B receptors [22]. Macitentan achieves a high affinity for the lipophilic milieu, with a 40- and 2000-fold increased affinity for the lipid phase versus bosentan and ambrisentan (another more ET-A selective ERA), respectively, and has superior pre-clinical in vivo efficacy [23]. Furthermore, the duration of action of macitentan was approximately 40 h at its maximal effective dose, double that of bosentan [24].

SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) was a multicentre, double-blind, randomised controlled trial assessing the effect of macitentan on morbidity and/or mortality in PAH patients [25]. The primary endpoint was the time from initiation of treatment. This was either placebo, 3 mg of macitentan, or 10 mg of macitentan to time of first occurrence of a composite endpoint of worsening of PAH, initiation of intravenous or subcutaneous prostanoids, lung transplantation, atrial septostomy, or death. The SERAPHIN population included 62 PAH-CHD patients. Analysis overall showed a significant improvement in the time to clinical worsening and 6MWD in those with combination therapy [26].

The Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity (MAESTRO) global trial enrolled 226 ES patients. Initial analysis showed that there was no significant improvement in the primary endpoint of exercise capacity (6MWD) but of note there was a decrease in this endpoint in the placebo group. There was however significant decrease in NT-pro-BNP levels (by 20%), reduction in PVR (by 13%), and good tolerability of the drug in the haemodynamic invasive substudy, advocating for further studies to evaluate the role of macitentan in the management of ES and other forms of PAH-CHD [27]. Prospective non-randomised data are providing promising signals on the safety and efficacy for macitentan in PAH-CHD [28, 29]. Although the data is not fully convincing, Macitentan remains a useful therapy for its other benefits, being once a day usage and reduced drug-drug interactions. The combination of macitentan and tadalafil (Optima study) showed significant improvement in outcomes, with a reduction in PVR of 47% along with similar improvements in NT-proBNP and 6MWD [30].

Prostacyclin pathway
Predominantly produced by endothelial cells, prostacyclin originates from the eicosanoid family of mediators, which also include prostaglandins, leukotrienes, and thromboxanes. Prostacyclin is the most potent endogenous inhibitor of platelet aggregation with cytoprotective and antiproliferative properties [31]. It works by activating cell surface receptors and cytosolic peroxisome proliferator-activated receptors. For prostacyclin, the preferred cell surface receptors are the IP receptors, which originate from G protein-coupled receptors. IP receptors are coupled to the activation of adenylate cyclase, allowing the conversion of adenosine triphosphate to a second messenger, cyclic adenosine monophosphate (cAMP). Through the activation of the cAMP-dependent protein kinases, this powerful messenger exerts different effects on various tissues, including vasorelaxation in vascular smooth muscle and inhibition of thrombosis, by acting on platelets.

In PAH, we see an imbalance between vasodilators, such as prostacyclin, which are lacking, and vasoconstrictors, which are in excess. Prostacyclin and other related drug analogues have undeniably revolutionised

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the treatment of PAH since their discovery in the 1970s, but their use in PAH-CHD has been limited by adverse effects and, in the case of intravenous prostacyclins, the need for an indwelling central venous line, with the associated risk of thrombosis and paradoxical embolism. For this reason, drugs acting on the prostacyclin pathway are restricted to PAH patients in WHO functional class III or IV, with rapid disease progression and/or lack of response to oral therapies. Therapies targeting the prostacyclin pathway have been available for many years, starting with epoprostenol in PAH-CHD [32–34].

Iloprost is a stable analogue of prostacyclin that can be administered intravenously or by inhalation, avoiding many of the systemic side effects associated with intravenous administration. Aerosolisation of prostacyclin has been shown to cause selective but short-lived pulmonary vasodilatation, increased cardiac output, and subsequently improve oxygenation in patients with PAH [35]. Like prostacyclin, iloprost has vasodilatory and antiplatelet effects, but has a longer plasma half-life of 20 to 30 min; moreover, its improved solubility in saline enables administration by intermittent nebulisation [36–38]. Designed to combine the beneficial long-term effects of continuous infusion of intravenous prostacyclin with the benefits of inhaled nitric oxide, iloprost has been classed as a promising agent for patients with PAH, but strong data are lacking. Skoro-Sajer et al. reported on the use of subcutaneous treprostinil, avoiding the need for indwelling central venous lines in a cohort of 32 WHO functional class III or class IV patients with ES (see Table 1) [44]. Patients had demonstrated lack of response to bosentan or had not yet started this ERA. WHO functional class improved significantly as did BNP levels and PVR.

Selexipag is a new oral IP receptor agonist, which appears to be effective in PAH, including patients with repaired CHD [47, 48]. The randomised controlled GRIP HON study included 110 patients with corrected CHD [49]. The composite primary outcome of mortality and morbidity was significantly improved by selexipag therapy and it was well tolerated in this subgroup [50].

Determinants of successful treatment
The aims of PAH therapies are well described in the European Guidelines [19] with a wish to move patients from high to lower risk. A combination of two agents, such as a PDE5i and an ERA, appears more likely to reduce the mortality, aiming to shift patients towards the "green" low risk zone for the clinical indices. At the current time, most clinicians will opt for a combination of PDE5i and ERA upfront or in rapid succession in order to achieve treatment goals as fast as is reasonable, within current commissioning and reimbursement guidelines.

Assessing suitability of different therapies for groups of PAH-CHD
With recent successes in clinical trials, the treatment for PAH-CHD patients has evolved progressively. Over the last decade, advanced PAH-specific therapy has become widely adopted in the treatment of PAH-CHD, especially ES, and for those with closed defects. Risk stratification remains a pivotal part of assessing suitability of treatment, response and timing of intervention, as well as disease progression and prognosis [51] . The WHO functional classification, despite its interobserver variability, remains one of the most widely used predictors of survival at diagnosis and subsequent follow-up. Other important predictors include 6MWD, peak oxygen uptake, markers of right ventricular (RV) dysfunction, haemodynamics, biomarkers and imaging.

Clinical assessment remains a pivotal part of managing these challenging cohorts as it provides valuable information in determining disease severity, improvement, stability, or deterioration. Elementary parts of the history should gauge important symptoms such as chest pain, changes in exercise tolerance, arrhythmia, syncope, and haemoptysis. Other important physical signs to look out for are the presence and severity of cyanosis, jugular venous pressure, oedema, ascites, and systemic blood pressure. Echocardiography is an important follow-up tool, as RV function is one of the key determinants of exercise capacity and prognosis in patients with PAH and there are now well described predictors of outcome [52].

Group A – Eisenmenger syndrome
Due to the complexity and severity of ES, usually augmented by systemic complications and comorbidities, determination of best treatment strategy remains a huge challenge. The BREATHE-5 trial was one of the first and largest trials of therapy in PAH-CHD. It showed that treatment with bosentan was safe in this group of patients [20]. However, no head-to-head studies have ever been performed to decide which therapy is the most efficacious in PAH-CHD. Most studies have been small observational studies using tadalafil and sildenafil [12, 14].

In a retrospective study, a cohort of 79 ES patients treated in a single institution for a period of up to 8.9 years was presented [53]. PAH therapies consisting of bosentan, sildenafil, sitaxentan, ambrisentan, tadalafil and inhaled iloprost as monotherapy, dual therapy, and triple therapy. It is noteworthy that due to the progressive nature of ES, 18 patients (23%) required up titration of therapy or introduction of dual or triple therapy after a median period of 2.5 years. A further observation from this study was that oxygen saturation during exercise improved with PAH therapy, indicating possible improvement in tissue oxygen delivery, which is likely to result in better exercise capacity. This study suggests that PAH

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Table 1 Published studies of therapies in ES (from [39])

Class	First author	Year	Drug	N	FC % change II/III/IV or mean	RCT	Main findings
ERA	Galiè [20]	2006	Bosentan	54	0/100/0	Yes	↓PVRi, ↓mPAP,↑6MWD
	Zuckerman [40]	2011	Ambrisentan	17	NR	No	↑6MWD
	Blok [28]	2017	Macitentan	40	52/48/0	No	↓FC, ↓NT-proBNP, ↔6MWD
	Herbert [29]	2017	Macitentan	15	NR	No	↑6MWD, ↑SaO$_2$
	Galie [41]	2017	Macitentan	226	60/40/0	Yes	↔6MWD, ↓NT-proBNP, ↓PVRi
PDE5i	Mukhopadhyay [7]	2006	Sildenafil	16	69/31/0	No	↑6MWD, ↑SaO$_2$, ↓mPAP, ↓PVR
	Chau [42]	2007	Sildenafil	7	3.3 ± 0.7	No	↓FC, ↑SaO$_2$, ↓mPAP, ↓PVR
	Garg [10]	2007	Sildenafil	21	46/54/0	No	↓FC, ↑6MWD, ↑SaO$_2$, ↓mPAP, ↓PVRi
	Tay [11]	2011	Sildenafil	12	0/100/0	No	↓FC, ↑6MWD, ↑HRQOL
	Zhang [12]	2011	Sildenafil	84	52/39/8	No	↑6MWD, ↑SaO$_2$, ↓mPAP, ↓PVRi
	Mukhopadhyay [14]	2011	Tadalafil	28	79/21/0	Yes	↓FC, ↑6MWD, ↓PVR
	Sun [13]	2013	Sildenafil	29	NR	No	↓FC, ↑6MWD, ↓PVR
Prostanoid	Rosenzweig [32]	1999	Epoprostenol (intravenous)	20	15/50/35	No	↓mPAP, ↑CI, ↓PVRi,↑SvO$_2$
	Fernandes [33]	2003	Epoprostenol (intravenous)	8	0/25/75	No	↑6MWD
	Thomas [43]	2013	Epoprostenol (intravenous) & Treprostinil (subcutaneous)	9	12/88/0	No	↓mPAP, ↑SvO$_2$
	Skoro-Sajer [44]	2018	Treprostinil (subcutaneous)	22	0/47/53	No	↓FC, ↓PVR, ↓NT-proBNP, ↑6MWD
	Yang [36]	2012	Iloprost (nebulised)	12	0/75/25	No	↓FC, ↑6MWD, ↑SaO$_2$,
	Cha [37]	2013	Iloprost (nebulised)	13	0/69/31	No	↓FC, ↑6MWD, ↑HRQoL
	Chon [38]	2017	Iloprost (nebulised)	11	0/64/36	No	↓FC, ↓mPAP, ↓PVR, ↑SaO$_2$, ↑6MWD
Combination	Iversen [45]	2010	Bosentan +/− Sildenafil	21	43/48/5	Yes	↔6MWD, ↑SaO$_2$
	D'Alto [46]	2012	Bosentan & Sildenafil	32	2.9 ± 0.3	No	↓FC,↑6MWD, ↓mPAP, ↓PVR, ↓NT-proBNP
	Sitbon [30]	2020	Macitentan & Tadalafil	46	63% improved FC	No	↓PVR, ↓NT-proBNP

Abbreviations and legend. CI: Cardiac index, FC: Functional class, HRQoL: Health related quality of life, mPAP: mean pulmonary artery pressure, NT-proBNP: N terminal pro-Brain natriuretic peptide, PVR(i): Pulmonary vascular resistance (indexed), SaO$_2$: peripheral oxygen saturation, 6MWD: 6 min walk distance, SvO$_2$: mixed venous oxygen saturation ↑: Increased, ↓:Decreased, ↔: No change

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therapies can have a long-standing beneficial effect in patients with ES with simple defects and may improve survival [54].

Expert centres may also use PAH-therapies in ES patients with complex anatomy and segmental pulmonary hypertension [55]. The use of advanced PAH-specific therapy has, however, not been formally assessed in ES patients with univentricular circulation (e.g. double inlet left ventricle) as many RCTs have excluded these complex patients due to difficulties in estimating PVR. However, there is evidence for use in complex diseases, but more detailed studies are needed [56–59]. Theoretically, using advanced therapy to increase pulmonary blood flow (Qp) may result in a reduction in peripheral cyanosis and improve oxygen delivery. However, caution must be exercised as significant increase in Qp can lead to volume overload in the single ventricle supporting both the systemic and pulmonary circulation and may precipitate ventricular dysfunction. As data are lacking, no strict recommendations can be put forward and decisions should be made on an empiric basis.

Group B – left to right shunts

In this group, PH is less severe than in ES patients and is associated with left-to-right shunt [60]. Cardiac catheterisation is used to decide which patients may be referred for surgical or interventional shunt closure. No prospective data is available on the use of invasive pulmonary vasoreactivity in determining outcome or suitability for repair [61]. In the case of correctable CHD, timely surgical repair is paramount in preventing

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pulmonary vascular disease, as early changes in the pulmonary vascular bed are likely to be reversible following shunt repair. In general, patients with prevalent systemic-to-pulmonary shunts and normal PVR can safely undergo shunt closure, whereas when PVR is mildly raised, expert opinion should be sought. European PH guidelines [51] recommend a PVR index (PVRi) of < 4 WU.m^2 (PVR < 2.3 WU) as the haemodynamic upper limit for operability in patients with atrial septal defect (ASD) or ventricular septal defect (VSD), thus discouraging shunt closure in cases of severe PAH with some caution for those with PVRi of between 4 and 8 WU.m^2. The use of PVRi is not clearly advantageous. With the increase in population body weights, significant numbers of people have an increase in body mass index, but this may be due to additional body fat, rather than increased size of the pulmonary or systemic circuit. At present, there are no established markers of reversibility, nor evidence-based algorithms to guide assessment for operability in this group of patients and decisions should be made on a case-by-case basis in tertiary centres with expertise in PAH-CHD. While some atrial level shunts serve as a potential relief valve in patients with severe PH, we await future results on the optimal fenestration size.

Considerations for shunt closure should also include, beyond PVR, type of defect, the PVR:systemic vascular resistance (SVR) ratio, as well as the systemic to pulmonary flow (Qp:Qs) ratio [62].

Group C - PAH with coincidental CHD (small defects)
In patients with PAH with small defects (typically VSD < 1 cm and/or ASD < 2 cm of effective diameter assessed by echocardiography), the clinical picture has been described to be very similar to patients with idiopathic PAH (IPAH). In most recent large trials of PAH therapies, patients are on combination medication.

Group D – post-operative PAH
Patients with postoperative PAH are also pathophysiologically very similar to patients with IPAH. Therefore, these patients should be treated according to current PAH guidelines [51]. In a retrospective study on the different clinical groups of PAH-CHD patients, the lowest survival was observed in patients with small/coincidental defects and post defect repair [63]. The 15-year survival of groups with small defects (66%) was even worse when compared to patients with ES (87%) (Table 2), which suggests that the lack of a 'blow off valve' to relieve right ventricular strain worsens prognosis in such patients.

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Conclusion
ES or one of the other forms of PAH-CHD, represents a severe condition that is associated with considerable morbidity and limited life expectancy. More children born with CHD are advancing into adulthood as a result of advancements in medical care. As such, there is an urgent need for optimisation of care in this population of adults, who are susceptible to disease-related complications.

Current available PAH-specific treatments include a variety of agents covering different mechanisms of action: PDE5i's, sGC stimulators, ERAs, prostacyclin analogues and prostacyclin receptor agonists. This review found that bosentan, riociguat, epoprostenol and sildenafil were all capable of improving functional capacity and haemodynamic parameters in patients with PAH-CHD but whether this corresponds with improved mortality remains to be seen, with only epoprostenol shown to have better survival rates. A combination therapy of ERA and PDE5i can be considered in order to improve outcomes in the former group of patients.

It is pivotal to recognise the unique pharmacological characteristics of drugs within each class and the specific evidence supporting the use of each treatment. Continued research to quantify the value of earlier treatment and combined regimens of targeted PAH therapies are likely to complement current insights and potentially revolutionise the treatment of PAH-CHD.

Table 2 Criteria for closing cardiac shunts in PAH-CHD (from [51])

Pulmonary vascular resistance		Recommendations	Class of evidence	Level of evidence
PVRi (WU.m^2)	PVR (WU)	Correctable*		
< 4	< 2.3	Yes	IIa	C
> 8	> 4.6	No	IIa	C
4–8	2.3–4.6	Individual patient evaluation in tertiary centres	IIa	C

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Abbreviations
ASD: Atrial septal defect; cAMP: Cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; CHD: Congenital Heart Disease; CTEPH: Chronic thromboembolic pulmonary hypertension; ERA: Endothelin receptor antagonist; ES: Eisenmenger syndrome; ET-A or ET-B: Endothelin receptor type A or type B; NO: Nitric oxide; NT-pro-BNP: N Terminal pro Brain type natriuretic peptide; PAH: Pulmonary Arterial Hypertension; PDA: Persistent arterial duct; PDE5i: Phosphodiesterase type 5 inhibitor; PVR(i): Pulmonary vascular resistance (indexed); Qp: Pulmonary blood flow; Qs: Systemic blood flow; sGC: Soluble Guanylate cyclase stimulator; SVR: Systemic vascular resistance; VSD: Ventricular septal defect; WHO: World Health Organisation; 6MWD: Six-minute walk distance

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